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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Applicant	:	Thierry BOON-FALLEUR et al.
Serial No.	:	08/819,669
Filed	:	March 17, 1997
For	:	TUMOR REJECTION, ANTIGEN PRECURSORS, TUMOR REJECTION ANTIGENS AND USES THEREOF
Art Unit	:	1644
Examiner	:	P. Gambel

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL
(37 CFR §1.192)

Pursuant to 37 C.F.R. §1.192, Applicants appeal from the rejection dated March 2, 2004. Applicants claims have been rejected more than twice, so appeal is proper.

Pursuant to 37 C.F.R. § 1.192, this Brief on Appeal is filed, in triplicate, and the fee required by 37 C.F.R. § 1.17(c), i.e., $320.00, accompanies this Brief.

I REAL PARTY IN INTEREST

The Real Party in Interest is Ludwig Institute for Cancer Research, the Assignee of the subject application.

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II RELATED APPEALS AND INTERFERENCES

To the best of the knowledge of appellants and appellants' legal representative, there are no pending appeals or interferences which will directly affect or be directly affected by, this appeal.

III STATUS OF CLAIMS

Claims 183-191 are pending and have been rejected. A copy of pending claims 183-191 is appended hereto.

Claims 1-182 have been canceled.

IV STATUS OF AMENDMENTS

All amendments have been entered. None are currently pending.

V SUMMARY OF THE INVENTION

The invention, which is the subject matter of the claims on appeal, is a family of proteins known as the MAGE tumor rejection antigen precursors. The acronym "TRAP" is used to refer to "tumor rejection antigen precursor," and will be used hereafter.

TRAPs are described in brief at page 6, lines 19-26 of the specification. TRAPs constitute a family of proteins which are expressed in tumor cells but not in normal cells*.

The TRAPs are processed, intracellularly, to generate small peptides, known as tumor rejection antigens, or "TRAs." TRAs are described at page 4, line 19 – page 5, line 14 of the specification. Briefly, the TRAs form complexes with MHC molecules, such as HLA molecules, with the resulting complexes forming a target for recognition by cytolytic T cells, i.e., "CTLs." Upon recognition of a complex of a TRA and an MHC molecule, the CTLs are stimulated to proliferate, and lyse the cell which present the TRA/MHC complex. See page 4, line 26 – page 5, line 3 of the specification.

Unquestionably, there are several types of molecules which are characteristic of cancer cells. For example, page 2, lines 1-22 of the specification refers to TSTAs, which are molecules produced when cells are mutated via chemical processes.

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* Subsequent to the invention, it was found that testis cells express TRAPs, but do not present tumor rejection antigens. This is elaborated upon, infra.

A second family of molecules characteristic of cancer cells are the "tum-" antigens, which are discussed at page 3, in its entirety. The tum- antigens and TSTAs differ from TRAPs, however. Page 5, last two lines, through page 6, line 18 of the specification, explain how TRAPs and TRAs are NOT the product of mutagenesis. See page 6, lines 1-2, for example.

Due to their expression in tumor cells, and lack of expression in normal cells, TRAPs serve as "markers" for cancer cells, in at least two ways. First, their presence indicates with almost complete certainty that the cell expressing the molecule is a cancer cell. In the isolated case of testis cells, it is well known that these lack MHC molecules, so TRAs cannot be presented by these cells, and thus a T cell proliferative response is not possible.

With respect to the subject invention, an exhaustive set of experiments were carried out, leading to the identification of the first member of the MAGE family, i.e., MAGE-1. Examples 17-22, over pages 33-41 discuss the characteristics.

Additional TRAPs were identified in these experiments, as is elaborated upon in example 23, at pages 41-42. This example also explains the derivation of the name MAGE.

Examples 24-28 characterize these molecules further, and discuss the close relationships amongst MAGE-1, 2, and 3.

The fact that these three MAGE TRAPs, i.e., MAGE-1, 2, and 3, were part of a larger family, is discussed in experiments set forth at page 29, including Southern Blotting. At page 47, the definition of stringent conditions recited in the claims is provided.

Example 30 describes the isolation and characterization of MAGE-4. Example 31, that of MAGE-5. Example 32 discusses MAGE-6, and example 33, the isolation of MAGE-7, 8, 9, 10, and 11.

All of these molecules were isolated and characterized using the conditions set forth in the claims. From the above referenced disclosure, one can list the following characteristics of MAGE TRAPs:

(i) they are proteins that are encoded by naturally occurring, non-mutagenized genes;

(ii) they are characteristic of cancer cells, and are not expressed by normal cells (with the exception of testes cells);

(iii) they are all encoded by nucleic acid molecules which hybridize to a reference sequence, i.e., one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions, and,

(iv) they are processed, intracellularly, into TRAs, i.e., peptides, which complex to MHC molecules to form targets for CTLs.

The present specification describes one TRA, which is a peptide that results from intracellular processing to form a complex with HLA-A1 molecules. This TRA consists of SEQ ID NO: 26. Example 34 describes the identification of this TRA. The TRA was patented in the parent application, i.e., U.S. Patent No. 5,925,729. Claims 184, 187 and 190 all require this peptide to be present as part of the claimed TRAP molecule.

A later filed application issued as U.S. Patent No. 5,405,940, describing and claiming TRAs from additional MAGE TRAPs, i.e., MAGE-2 – MAGE-6.

The peptides of the '729 patent and the '940 patent form complexes with HLA-A1 molecules; however, additional TRAs have been found within the MAGE TRAPs, which form complexes with different MHC molecules. A partial listing of such TRAs is provided in an Appendix to this Brief.

VI SUMMARY OF ISSUES

A. Did the Examiner err in deeming claims 183-191 to fail to satisfy the Written Description Requirement, under 35 U.S.C. § 112, first paragraph?

B. Did the Examiner err in deeming claims 183-191 to fail to satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph?

It is Appellant's contention that both "A" and "B" are correctly answered in the affirmative.

There is, potentially, a third issue, i.e., a double patenting issue. As is discussed, infra, there is an extensive discussion of double patenting in the Office Action appealed from, but no rejection is presented. In the interest of expediting this application, however, applicants are submitting a terminal disclaimer herewith.

VII GROUPING OF CLAIMS

The claims do not rise or fall together. Rather, claims 183, 185, 186, 188, 189 and 191 will be grouped together. Claims 184, 187, and 190 will be grouped together.

The reasons for this grouping will be set forth in VIII, infra, as is permitted by 37 C.F.R. § 1.192.

VIII ARGUMENT

A. The Rejection of Claims 183, 185, 186, 188, 189, and 191 for Failing to Satisfy the Written Description Requirement of 35 U.S.C. § 112, First Paragraph, is Erroneous, and Should be Reversed

The written description requirement is based upon 35 U.S.C. § 112, i.e.:

> "The specification shall contain a written description of the invention, and of the manner and process of using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

It has long been established that the determination of whether or not a claimed invention complies with the written description requirement is a fact based inquiry. See Enzo Biochem Inc. v. Gen-Probe Inc., 63 USPQ2d 609, 612 (Fed. Cir. 2002); Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991); In re DiLeone, 168 USPQ 592, 593 (CCPA 1971). As such, it is helpful to begin analysis of this application with a review of the relevant facts.

At the time the application was filed, it disclosed that a gene family was suggested by the data, which included Southern Blotting. See, e.g., Example 29 of the specification, referring to figure 12. The 2.4 kilobase probe discussed in example 29 is described, and sequenced, in example 20. This comprises MAGE-1, which the Examiner agrees is described in the specification. Experiments using this probe described in example 23, identified two additional family members, i.e., MAGE-2 and MAGE-3. As was pointed out, supra, the 2.4 kilobase probe

(MAGE-1), also serves to identify MAGE-4, 5, 6, 7, 8, 9, 10, and 11. As example 29 sets forth, all hybridization was carried out under stringent conditions, which are defined in example 29.

Figure 13 provides information on the structure of some of these MAGE coding sequences. The homology is clear. Also clear is the fact that experiments showed no expression in normal tissues, coupled with expression in cancer. Please note figures 11A and 11B.

Thus, the examples provide eleven species, all of which satisfy the language of the claims.

The Examiner's position appears to be set forth at page 2, i.e.:

> "Here the specification does not provide sufficient written description of MAGE tumor antigen precursors as broadly claimed based upon the limited disclosure/recitation of a limited number of nucleic acids encoding a specific MAGE-1, MAGE-2, or MAGE-3. There is insufficient written description of the structural attributes that define or distinguish a MAGE tumor rejection antigen precursor, including MAGE-1 tumor rejection antigen precursors, from one another or other molecules."

It is believed that this basis for a rejection is flawed, for a number of reasons.

First of all, it ignores relevant facts. While MAGE-1, 2, and 3 do in fact, satisfy the criteria of the claims, they are not the only molecules which do. As has been articulated supra, and at many points during the extended prosecution, MAGE-1 - 11 are encompassed by the claims and are described in the specification.

Second, the Examiner asserts that insufficient structural attributes are given, therefore, the claims do not satisfy the written description requirement.

In fact, the correct standard is the following:

> "Written description may be satisfied through disclosure of relevant identifying characteristics, i.e., structure, other physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

Enzo, supra at 1613, referring to the USPTO's internal Guidelines for Written Description. Indeed, the Federal Circuit in Enzo stated:

> "We are persuaded by the Guidelines in this point and adopt the PTO's applicable standard for determining compliance with the written description requirement."

Enzo, ibid. Hence, the Examiner has failed to apply the correct standard in looking only for structural correlation.

Even assuming arguendo that structural similarity is the sole criterion for determining compliance with the written description requirement, the recitation of the hybridization conditions in the claims, which is in accordance with standard procedure, coupled with the evidence of 11 species, satisfies the written description requirement. Again, with reference to Enzo, at 1615:

> "The PTO has also provided a contrasting example of genus claims to nucleic acids based upon their hybridization properties, and has determined that such claims may be adequately described if they hybridize under highly stringent conditions to known sequences, because such conditions dictate that all species within the genus will be the same."

Enzo at 1615.

The Examiner states that there is insufficient information given to distinguish MAGE molecules form each other, or from other molecules, i.e.:

> "There is insufficient written description of the structural attributes that define or distinguish a MAGE tumor rejection antigen precursor, including a MAGE-1 tumor rejection antigen precursors from one another or other molecules."

These remarks are not understood. The issue raised by the Examiner, in connection with written description and the alleged lack thereof, is that there isn't sufficient unifying structural information. Now, the Examiner says that this information is present, but that there is too much.

With respect to the alleged inability to distinguish MAGE molecules from other molecules, the Examiner has proffered no evidence of this.

Ironically, immediately after stating that there is insufficient information to distinguish the MAGE TRAPs from each other, the Examiner states:

> "(I)t is noted that the structure (e.g., sequences) of MAGE molecules differ from one another."

Applicants admit the molecules differ from each other. Members of a genus do. They are similar to each other, such that their complements hybridize to each other under stringent conditions.

Similarity is not identity; however, when nucleic acid molecules share common structural features, their complements will hybridize to each other. That is in fact a common structural feature, uniting what is claimed.

The Examiner follows this argument with citation, and reliance on Ding, et al., *Biochem. Biophys. Commun.*, 202:549-555 (1994), and argues that:

> "Ding et al. discloses that homologous MAGE-1 can be polymorphic."

Again, the relevance of this reference, and the point made by the Examiner, are not clear. Applicants do not disagree that MAGE-1 can be polymorphic. Indeed, if they did NOT believe that it could be polymorphic, there would be no reason to claim the subject matter by way of hybridization. One would claim the specific sequence, and no more.

In terms of written description, however, the issue is: does the specification adequately describe the claimed polymorphisms which fall under the language of the stringent conditions of hybridization?

The Ding reference teaches MAGE-1 sequences which differ from the reference sequence by two nucleotides. This was pointed out in, e.g., applicants Amendment dated December 31, 2002. The quotation from Ding is repeated here:

> "A gene highly homologous to MAGE-1 was isolated which differs from the published DNA sequence at positions 94 and 813. The position 94A to G transition result in a threonine to alanine substitution while the position 813 mutation is silent."

In other words, there are two differences with reference to SEQ ID NO: 8. The MAGE molecules which were found via hybridization with SEQ ID NO: 8 at the recited conditions, and which are disclosed in the specification, differ from SEQ ID NO: 8 by more than two nucleotides. Nonetheless, they hybridized to SEQ ID NO: 8, i.e., the specification did describe them. Does it not follow that a sequence more closely related to the reference sequence will also hybridize thereto, and is thus adequately described?

Applicants have made this argument to the Examiner, and have not had a response other than the argument is "not persuasive." Why it is not persuasive is absent from the record.

The Examiner then turns to Brasseur, et al. *Int. J. Cancer*, 52:839-841 (1992). Again, it is not at all clear why this reference has been cited. The Examiner points to statements that are made in Brasseur, that Northern Blotting does not permit the artisan to distinguish amongst the

members of the MAGE family, but PCR did allow differentiation. How this is relevant to an alleged lack of written description is unexplained, and undeveloped.

In any event, applicants contest the very citation of Ding and Brasseur.

The subject application claims priority to May 23, 1991. Priority has never been questioned, challenged, or otherwise brought into question. Brasseur was published in 1994, and Ding in 1992.

In In re Koller et al., 204 USPQ 702, 707 (CCPA 1980), the predecessor Court to the Court of Appeals for the Federal Circuit held:

> "In Hogan, an analysis using later-filed references to determine the scope of enablement was found to be impermissible. Similarly it cannot be allowed when, as here, the description requirement is at issue."
>
> (emphasis in the original).

Applicants are certainly aware of In re Wright, 27 USPQ2d 1510 (Fed. Cir. 1993), but note that (i) Wright did NOT overrule or distinguish Koller, and (ii) Wright does not deal with the written description requirement. As a matter of law, then, neither Brasseur nor Ding can be relied upon.

To the same end, reliance on Boon, et al., *Int. J. Cancer*, 54:177-180 (1993), Kirkin, et al., *APMIS*, 106:665-679 (1998), and DePlaen, et al., *Immunogenetics*, 40:360-369 (1994), are also relied upon improperly.

The Examiner, at page 4 of his action, points to the functions of the claims and states that the function:

> "depends, in part, upon the processing and presentation of MAGE-derived peptides in an attempt to obtain cytotoxic T cells directed against these peptides."

This argument is related to that made at page 3 as well.

Assuming, arguendo, that the Examiner's statement is true, it is pointed out that applicants nowhere state that this must be done in vivo. In fact, as the examples show, it not only can be done in vitro, it was done in vitro. Further, cytotoxic T cells are not useful only in an in vivo context. As the specification also makes clear, the CTLs can be used diagnostically.

Given these teachings, it is difficult to fathom the rationale behind the Examiner's citation of Boon, et al. *J. Cancer*, 54:177-180 (1993). According to the Examiner, this reference states:

> "(I)t is difficult to predict whether therapeutic success will be achieved, even if a significant increase in anti-tumor CTL is obtained by immunization."

Boon at 178, second column. How this is relevant to written description in this case is not seen. There are no method claims presented, such that therapy is contemplated by the claims. Nor does the reference suggest that one of ordinary skill in the art would not be able to ascertain the claimed invention from the disclosure.

Further, when an Examiner makes a reference of record, it must be considered for its full teachings, not just that part on which the Examiner relies. W.L. Gore & Assoc. v. Garlock, Inc., 220 USPQ 903 (Fed. Cir. 1983), cer't denied, 469 US 851 (1984). Further, the Federal Circuit has held that evidence in the art that supports, rather than negates patentability, must be considered. In re Dow Chemical, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988). Hence, it is relevant to note that the Boon reference states, at the very end of page 178:

> "The methods that have led to the identification of a first human gene coding for tumor rejection antigens should soon lead to the identification of others."

It is this statement which is more relevant to the present case than that cited by the Examiner. It shows that, contrary to the Examiner's position, it was believed that one would some day identify and isolate relevant molecules, as the inventors did, in the present case.

Nor is it understood why the Examiner relies on Kirkin, et al., *APMIS*, 106:665-679 (1998), to support an alleged lack of written description.

First, it is pointed out that Kirkin, et al., is not prior art. Second, the Examiner points to "low immunogenicity of the MAGE antigens" as well as other features which allegedly raise issues with respect to the molecules.

First, with respect to the degree of immunogenicity, since this is not a feature of the claims, it is irrelevant. There is no requirement that an immunogenicity molecule posses a low, intermediate, or high degree of immunogenicity. Further, if Kirkin, as a non-prior art reference is going to be considered, then applicants must be permitted to rebut the statements, with additional non-prior art materials. Attached hereto is a partial listing of the literature on MAGE

TRAPs, showing that the molecules are, in fact, immunogenic. Any argument that the molecules are not immunogenic, or are poorly immunogenic, is clearly wrong.

The Examiner cites to yet another, non-prior art reference, i.e., Stevenson, *FASEB J.*, 5:2250-2257 (1991), arguing that:

> "Defining human tumor antigens or tumor antigen precursors has not been readily apparent to the skilled artisan."

Stevenson speaks of the original definition of a tumor specific transplantation antigen, and states that "attempts to delineate tumor antigens in human tumors apart from the virally encoded antigens have been fraught with difficulty."

While the Examiner has not provided any explanation of why or how this reference supports the view that written description is lacking, applicants have in fact provided a discussion of the terminology used in the field, as well as an explanation of how the invention is different. Page 2, lines 1-17 discuss the "TSTAs" of references like Stevenson. The specification goes on to discuss other families of tumor antigens, over pages 2-4, with the defining characteristics of TRAs, and TRAPs, set forth at page 4, lines 18 - page 6, end. As applicants have acknowledged the issue, and addressed it in the specification supporting their invention, clearly distinguishing the invention from the art, it is not seen how Stevenson is relevant.

Nor is Boon, et al., *Cancer Cells*, 1:25-28 (1989), any more relevant. Boon et al. discuss the tum- antigens, but again, the specification explains, quite clearly, how these differ from what is claimed.

With respect to the Examiner's statement, i.e.:

> Therefore, the skilled artisan recognized the difficulty in defining a human tumor antigen at the time the invention was made and recognized the requirement to demonstrate its existence."

and

> "In addition to defining human tumor antigens, the skilled artisan recognized the difficulties in defining a MAGE tumor rejection antigen precursor given the homology and diversity of MAGE molecules and given the lack of correlation with between (sic).

With respect to the first comment, the Examiner speaks of the "homology and diversity" of MAGE molecules, and argues that the art shows these qualities made it difficult to define a MAGE TRAP.

To the contrary, as was shown in the specification, and has been pointed out, over and over again, the homology permits one of ordinary skill to define the invention in the manner defined in the application and to understand what is meant. Applicants agree that there is diversity amongst the family members, but every family of molecules will show diversity therebetween. The Examiner also points to an alleged lack of correlation between structure and the ability to generate anti-tumor CTLs in vivo. This has not been shown. Further, since the claims do not require in vivo efficacy, the argument is not on point.

With respect to the second comment, applicants respectfully traverse. It is not uncommon to define nucleic acid molecules structurally, by means of their ability to hybridize to specific molecules. All of the species described in the specification meet the criteria of the claims.

The Examiner then argues that only SEQ ID NOS: 7 and 8 satisfy the written description requirement, and relies on various cases and the "Guidelines For the Examination of Patent Applications." Specifically, the Examiner cites to Vas-Cath v. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991), and The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1406 (Fed. Cir. 1997). It is submitted that neither case supports the Examiner's position, although it is agreed that the Vas-Cath case makes clear that the written description and enablement requirements are separable.

The Vas-Cath case cites In re Driscoll, 195 USPQ 1245, 1250 (CCPA 1977), with approval:

> "(I)t should be readily apparent from recent discussions of this court involving the question of compliance with the description requirement of § 112 that each case must be decided on its own facts. Thus the precedential value of cases in this area is extremely limited."

Vas-Cath at 1116, citing In re Driscoll. The Vas-Cath court went on to state:

> "Although [the applicant] does not have to describe exactly the subject matter claimed...the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."

In the present case, the claims provide a reference sequence, and employ hybridization conditions that are clearly cognizable to one of ordinary skilled in the art. The invention is clearly described in the application as filed, which was NOT the case in Vas-Cath. Vas-Cath involved a situation where an applicant was attempting to rely on an earlier filed application to support material added at a later point in time. These operative facts are not operative here.

Nor is the Eli Lilly case pertinent. Applicants agree that this case stated that "the description of a genus is achieved by a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus."

In contrast to the situation in Eli Lilly, where no sequences were disclosed, applicants have described sequences for MAGE-1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11. While it is agreed that there is no rule that a certain number of species must be disclosed, clearly the number disclosed here must be deemed to be a sufficient number.

The "Guidelines for the Examination of Patent Applications" are not to the contrary. A species (11), were reduced to practice. Relevant, identifying characteristics, i.e., the ability to hybridize to SEQ ID NO: 8, are shown and recited. Functional characteristics, i.e., the ability to generate CTLs, in vitro or in vivo, are described. As such, reliance on the Eli Lilly case is in appropriate, as the relevant fact of this case are clearly NOT on point with Eli Lilly.

For all of the following reasons, the rejection of claims 183, 185, 186, 188, 189, and 191 under 35 U.S.C. § 112, first paragraph, for failing satisfy the written description requirement, should be reversed.

B. The Rejection of Claims 184, 187, and 190 Under 35 U.S.C. § 112, First Paragraph, for an Alleged Failure to Satisfy the Written Description Requirement is Improper, and Should be Reversed

Each of claims 184, 187, and 190 require that the MAGE tumor rejection antigen precursor include the amino acid sequence of SEQ ID NO: 26. SEQ ID NO: 26 is a peptide consisting of 9 amino acids, which has been shown to function as a tumor rejection antigen, which forms a complex with HLA-A1 molecules, and stimulates proliferation of CTLs thereby Parent Application No. 08/142,368, which issued as U.S. Patent No. 5,925,729, issued with its single claim directed to this nonapeptide. Also see example 34 of the specification.

The amino acid sequence in question, i.e., Glu Ala Asp Pro Thr Gly His Ser Tyr, is conserved in the sequence "highly homologous" to MAGE-1, reported by Ding, and relied upon by the Examiner*.

With respect to the Examiner's arguments in support of a lack of written description, none are specifically directed to these claims; however, the Examiner's first argument is based on an alleged inability to distinguish MAGE molecules from other molecules.

Each of claims 184, 187, and 190 require that a specific amino acid sequence be present. It is believed that the Board can take judicial notice that it is within the level of skill of the artisan to determine an amino acid sequence, and hence to determine if the nonapeptide is present.

Similarly, to the extent the Examiner's arguments about differences in structure are relevant, these claims require commonality of structure. In other words, in addition to the properties listed in parent claim 181, claims 184, 187 and 190 all require that a specific structure be present.

Further, with respect to the Examiner's arguments regarding the alleged inability of the TRAPs to function, it is pointed out that the specification teaches, and the USPTO has accepted, the proposition that SEQ ID NO: 26 is a tumor rejection antigen. Additional references could be provided to show this as well.

The inclusion of the specific tumor rejection antigen sequence in claims 184, 187, and 190 makes it even more clear that these claims satisfy the written description requirement. Hence, for the reasons set forth in this section, as well as the arguments presented for claims 183, 185, 186, 188, 189, and 190 claims 184, 187, and 190 should be held to satisfy the written description requirement, and the rejection should be reversed.

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* The changes reported in Ding are a silent mutation, and one where threonine (Thr) becomes Alanine (Ala), due to a change at nucleotide 94. This occurs well before the sequence of SEQ ID NO: 26, which is at positions 169-177 of the MAGE-1 amino acid sequence.

C. The Rejection of Claims 183, 185, 186, 188, 189, and 191 As Failing to Satisfy the Enablement Requirement of 35 U.S.C. § 112, First Paragraph, Is Improper and Should be Reversed

The Examiner has rejected all pending claims under 35 U.S.C. § 112, first paragraph, as allegedly failing to satisfy the enablement requirement. It is believed that this rejection is improper and should be reversed.

As with the rejection based upon an alleged failure to satisfy the written description requirement, the rejection ignores the facts, does not explain why references are relied upon, and misstates applicable law.

For example, the Examiner states, at page 6:

> "While the recitation of tumor rejection antigen precursor may have some notion of the properties of the claimed molecule(s), claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make and use the 'tumor antigen precursor' commensurate in scope with the claimed invention."

One might assume from this quote that the claim reads, e.g.:

> "An isolated tumor rejection antigen precursor."

This is not the case. The claim defines the molecules that are claimed by way of the ability of nucleic acid molecules to hybridize to a defined, specified sequence, under defined conditions.

As was pointed out, supra, eleven such molecules are described by way of nucleotide sequences. All of these molecules were found via hybridization using reference sequence SEQ ID NO: 8, and at the conditions specified. Hence, the statement:

> "Applicant has not provided sufficient biochemical information (e.g., nucleic acid sequence) that distinctly identifies the breadth of MAGE tumor rejection antigens encoded by nucleic acids encoding tumor rejection antigen precursors which hybridize to SEQ ID NO: 8 encompassed by the claimed invention."

is simply inaccurate. As is pointed out, eleven sequences were identified via hybridization. Their sequences are provided. Protocols were provided in order to determine (i) if a given nucleic acid molecule hybridizes to SEQ ID NO: 8, and (ii) how to determine if such a molecule encodes a tumor rejection antigen precursor (this word is left out of the Examiner's statement).

The eleven molecules identified are not the same. There is a degree of difference, one from the other. Yet they all share the properties of tumor rejection antigen precursors, as defined in the specification.

In support of his position, the Examiner first relies on a non-prior art reference, i.e., Ding et al., discussed supra, for the position that "homologous MAGE-1 can be polymorphic."

The relevance of this statement cannot be determined because the Examiner has not explained it. Further, it does not prove a lack of enablement, and instead supports enablement.

Ding does show two differences between the "polymorphic" MAGE-1 and MAGE-1 as described in the specification; however, rather than saying that this molecule - or any of the other molecules described therein are not members of the MAGE family, Ding states that they are. Clearly, this is evidence that the state of the art was such that artisans recognized other members of the MAGE family, which satisfy the requisites of the claims - exist. (The Examiner never posits that the molecules disclosed by Ding would not hybridize to SEQ ID NO: 8.

The Examiner follows this with the statement:

> "Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to be a protein found in the sequence data bases."

The relevance of this statement escapes applicants, since they do not use sequence data bases, do not advocate them, and never state either in the specification or claims that the invention is defined by way of homology per se.

The Examiner cites to non-prior art Skolnick, et al. *Trends in Biotech.*, 16:34-39 (2000), to argue that protein structure does not permit one to determine function.

Actually, Skolnick's statements are not that broad. Skolnick discusses an analysis of computer data based for common structural features, and then draws conclusions. There is absolutely no evidence whatsoever that Skolnick et al. tested the nucleic acid molecules which encoded these proteins to determine whether or not these hybridized to a reference sequence, under any conditions at all. The lack of any empirical evidence renders Skolnick completely irrelevant, apart from its non-prior art status.

The Examiner turns to a second, non-prior art reference, i.e., Bork, *Genome Research*, 10:398-400 (2000), which discusses the error rate in computer data bases with respect to sequence analysis.

Again, the relevance of this reference is not seen. Applicants do not present claims based upon homology, do not refer to computer based analysis and do not exploit sequence data bases at all. Bork provides no teachings whatsoever on what one should expect in the context of molecules which hybridize to each other.

Smith, *Nature Biotechnology*, 15:1222-1223 (1997), which is also not a prior art reference, is cited for the proposition that "there are numerous cases in which proteins having very different functions show structural similarity due to evaluation from a common ancestral gene."

It is submitted that, even assuming this is the case, for purposes of enablement, the issue is: does the specification provide adequate information such that one of ordinary skill in the art would be able to distinguish molecules with the desired functionability from those which do not possess it? The specification does show how this can be done.

Further, as has been pointed out, applicants found eleven species which had the desired function, using methods described in the application. The art, as per Ding, for example, found several more.

There is absolutely no evidence of any molecules which satisfy the hybridization conditions but do not possess the recited properties of tumor rejection antigen precursors. The Examiner has merely provided non-prior art references which question the ability of computer based homology searches to find molecules of related functions, and as applicants have pointed out, supra, they do not employ such methods, and do not need to.

At page 7 of the Office Action, the Examiner states there is insufficient guidance to practice the invention, and concludes rather than proves, that one of ordinary skill in the art is not enabled to practice what is claimed.

It is submitted that this approach is not proper. A patent application is presumed to be enabled. In re Marzocchi, 169 USPQ 367 (CCPA 1971). If there is objective evidence to doubt the enablement of the claimed subject matter, the Examiner must provide it, and it must be evidence that existed as of the filing date of the application in question. In re Hogan, 194 USPQ 527, 538 (CCPA 1977). Nothing provided by the Examiner supports the contention the statements relied upon for enablement are incorrect, or in any way compromised.

At pages 8-10 of the Office Action, the Examiner essentially repeats precisely the same argument made in contending that the written description requirement is not satisfied. The

repetition of the argument, verbation, is ironic, since at page 6 of the Office Action, the Examiner states:

> "Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision."

This is certainly the case. Hence, applicants do not understand how an argument advanced to challenge written description can be repeated, verbation, in support of a lack of enablement rejection. Nonetheless, for the sake of completeness, applicants will again address these references.

As with the written description rejection, the Examiner cites Ding, et al., *Biochem. Biophys. Commun.*, 202:549-555 (1994), and argues that:

> "Ding et al. discloses that homologous MAGE-1 can be polymorphic."

Applicants have pointed out, supra that they do not disagree that MAGE-1 can be polymorphic. Indeed, if they did NOT believe that it could be polymorphic, there would be no reason to claim the subject matter by way of hybridization. One would claim the specific sequence, and no more.

For enablement purposes, however, the issue is: does Ding cost doubt on whether the claim scope is enabled.

The Ding reference teaches MAGE-1 sequences which differ from the reference sequence by two nucleotides. This was pointed out in, e.g., applicants Amendment dated December 31, 2002. The quotation from Ding is repeated here:

> "A gene highly homologous to MAGE-1 was isolated which differs from the published DNA sequence at positions 94 and 813. The position 94A to G transition result in a threonine to alanine substitution while the position 813 mutation is silent."

In other words, there are two differences in Ding's molecule, as compared to SEQ ID NO: 8. The MAGE molecules which were found via hybridization with SEQ ID NO: 8 at the recited conditions, and which are disclosed in the specification, differ from SEQ ID NO: 8 by more than two nucleotides. Nonetheless, they hybridized to SEQ ID NO: 8, i.e., the specification did describe them. Does it not follow that a sequence more closely related to the reference sequence will also hybridize thereto, and thus the claims are enabled? The citation to Ding is not

understood, since Ding actually supports enablement, by showing that molecules in addition to those described in the specification satisfy the claims.

Applicants have made this argument to the Examiner, and have not had a response other than the argument is "not persuasive." Why it is not persuasive is absent from the record.

The Examiner then turns to Brasseur, et al. *Int. J. Cancer*, 52:839-841 (1992). Again, it is not at all clear why this reference has been cited. The Examiner points to statements that are made in Brasseur, that Northern Blotting does not permit the artisan to distinguish amongst the members of the MAGE family, but PCR did allow differentiation. How this is relevant to an alleged lack of enablement is unexplained, and undeveloped.

In any event, applicants contest the very citation of Ding and Brasseur.

The subject application claims priority to May 23, 1991. Priority has never been questioned, challenged, or otherwise brought into question. Brasseur was published in 1994, and Ding in 1992.

In In re Hogan et al., 194 USPQ 527 (CCPA 1977), the predecessor Court to the Court of Appeals for the Federal Circuit held:

> "In Hogan, an analysis using later-filed references to determine the scope of enablement was found to be impermissible. Similarly it cannot be allowed when, as here, the description requirement is at issue."
>
> (emphasis in the original).

Applicants are certainly aware of In re Wright, 27 USPQ2d 1510 (Fed. Cir. 1993), but note that Wright did NOT overrule or distinguish Hogan. As a matter of law, then, neither Brasseur nor Ding can be relied upon.

To the same end, reliance on Boon, et al., *Int. J. Cancer*, 54:177-180 (1993), Kirkin, et al., *APMIS*, 106:665-679 (1998), and DePlaen, et al., *Immunogenetics*, 40:360-369 (1994), are also relied upon improperly.

The Examiner, at page 4 of his action, points to the functions of the claims and states that the function:

> "depends, in part, upon the processing and presentation of MAGE-derived peptides in an attempt to obtain cytotoxic T cells directed against these peptides."

This argument is related to that made at page 3 of the Office Action as well.

Assuming, arguendo, that the Examiner's statement is true, it is pointed out that applicants nowhere state that this must be done in vivo. In fact, as the examples show, it not only can be done in vitro, it was done in vitro. Further, cytotoxic T cells are not useful only in an in vivo context. As the specification also makes clear, the CTLs can be used diagnostically.

Given these teachings, it is difficult to fathom the rationale behind the Examiner's citation of Boon, et al. *J. Cancer*, 54:177-180 (1993). According to the Examiner, this reference states:

> "(I)t is difficult to predict whether therapeutic success will be achieved, even if a significant increase in anti-tumor CTL is obtained by immunization."

Boon at 178, second column. How this is relevant to enablement is not seen. There are no method claims presented, such that therapy is contemplated by the claims. Nor does the reference suggest that one of ordinary skill in the art would not be able to ascertain the claimed invention from the disclosure.

Further, when an Examiner makes a reference of record, it must be considered for its full teachings, not just that on which the Examiner relies. Hence, it is relevant to note that the Boon reference states, at the very end of page 178:

> "The methods that have led to the identification of a first human gene coding for tumor rejection antigens should soon lead to the identification of others."

It is this statement which is more relevant to the present case than that cited by the Examiner. It shows that, contrary to the Examiner's position, it was believed that one would some day identify and isolate relevant molecules, as the inventors did, in the present case.

Nor is it understood why the Examiner relies on Kirkin, et al., *APMIS*, 106:665-679 (1998), to support an alleged lack of enablement, anymore than it was understood why this reference allegedly supports the lack of written description requirement.

First, it is pointed out that Kirkin, et al., is not prior art. Second, the Examiner points to "low immunogenicity of the MAGE antigens" as well as other features which allegedly raise issues with respect to the molecules.

First, with respect to the degree of immunogenicity, since this is not a feature of the claims, it is irrelevant. There is no requirement that an immunogenic molecule posses a low, intermediate, or high degree of immunogenicity. Further, if Kirkin, as a non-prior art reference

is going to be considered, then applicants must be permitted to rebut the statements, with additional non-prior art materials. Attached hereto is a partial listing of the literature on MAGE TRAPs, showing that the molecules are, in fact, immunogenic. Any argument that the molecules are not immunogenic, or are poorly immunogenic, is clearly wrong.

The Examiner cites to yet another, non-prior art reference, i.e., Stevenson, *FASEB J.*, 5:2250-2257 (1991), arguing that:

> "Defining human tumor antigens or tumor antigen precursors has not been readily apparent to the skilled artisan."

Stevenson speaks of the original definition of a tumor specific transplantation antigen (TSTA), and states that "attempts to delineate tumor antigens in human tumors apart from the virally encoded antigens have been fraught with difficulty."

While the Examiner has not provided any explanation of why or how this reference supports the view that enablement is lacking, applicants have in fact provided a discussion of the terminology used in the field, as well as an explanation of how the invention is different. Page 2, lines 1-17 discuss the "TSTAs" of references like Stevenson. The specification goes on to discuss other families of tumor antigens, over pages 2-4, with the defining characteristics of TRAs, and TRAPs, set forth at page 4, lines 18 - page 6, end. As applicants have acknowledged the issue, and addressed it in the specification supporting their invention, clearly distinguishing the invention from the art, it is not seen how Stevenson is relevant.

Nor is Boon, et al., *Cancer Cells*, 1:25-28 (1989), any more relevant. Boon et al. discuss the tum- antigens, but again, the specification explains, quite clearly, how these differ from what is claimed.

With respect to the Examiner's statement, i.e.:

> Therefore, the skilled artisan recognized the difficulty in defining a human tumor antigen at the time the invention was made and recognized the requirement to demonstrate its existence."

and

> "In addition to defining human tumor antigens, the skilled artisan recognized the difficulties in defining a MAGE tumor rejection antigen precursor given the homology and diversity of MAGE molecules and given the lack of correlation with between (sic).

With respect to the first comment, the Examiner speaks of the "homology and diversity" of MAGE molecules, and argues that the art shows these qualities made it difficult to define a MAGE TRAP.

To the contrary, as was shown in the specification, and has been pointed out, over and over again, the homology permits one of ordinary skill to define the invention in the manner defined in the application and to understand what is meant. Applicants agree that there is diversity amongst the family members, but every family of molecules will show diversity therebetween. The Examiner also points to an alleged lack of correlation between structure and the ability to generate anti-tumor CTLs in vivo. This has not been shown. Further, since the claims do not require in vivo efficacy, the argument is not on point.

With respect to the second comment, applicants respectfully traverse. It is not uncommon to define nucleic acid molecules structurally, by means of their ability to hybridize to specific molecules. All of the species described in the specification meet the criteria of the claims.

The fact is, the references cited by the Examiner, Ding in particular, support enablement. They show that, after applicants identified eleven species which satisfy the parameters of the claims, others identified more molecules, which they identified as MAGE TRAPs, in accordance with the invention. No author has questioned the scope, language, or definition of MAGE, or the pioneering nature of applicants' invention. The Examiner, notwithstanding the plethora of references cited, has not carried the burden of proving lack of enablement, and the rejections should be reversed.

D. The Rejection of Claims 184, 187, and 190 as Failing to Satisfy the Enablement Requirement of 35 U.S.C. § 112, First Paragraph, Is Improper and Should be Reversed

As was pointed out in VIIIB, supra, claims 184, 187, and 190 require that the amino acid sequence set forth in SEQ ID NO: 26 be a part of the claimed TRAP. SEQ ID NO: 26 is a known, art recognized, tumor rejection antigen. It has been shown to be presented by HLA-A1 molecules, and to stimulate proliferation of CTLs, as a result.

The Examiner has not questioned this. The Examiner has not provided evidence of a single molecule which includes this amino acid sequence, but does not serve as a tumor rejection antigen precursor. In contrast, applicants have shown that molecules which contain it do.

Indeed, the Examiner has confessed that SEQ ID NOS: 7 and 8 are enabled. These include SEQ ID NO: 26.

The likelihood of the specific amino acid sequence defined by SEQ ID NO: 26 is $1:20^9$, because there are 9 amino acids in the sequence, and twenty amino acids available for each position.

These odds clearly subvert any concerns about molecules which do not satisfy the enablement requirement, because the only molecules shown to actually contain the specific sequence do function as tumor rejection antigen precursors. Again, a prima facie case has not been made out, and the rejection of claims 184, 187, and 190, should be reversed.

E. Is There a Rejection on Double Patenting Grounds?

At pages 11-14 of the Office Action, the Examiner discusses:

> (i) the general tenets of a double patenting rejection (point 5);
>
> (ii) argues that claims 1 and 2 of U.S. Patent No. 6,025,474 are not patentably distinct from present claims 183-191 (point 6);
>
> (iii) present boiler plate regarding interferences between commonly held patents and applications (point 7);
>
> (iv) argues that U.S. Patent No. 6,025,474, would serve as a basis for a rejection of the present claims if not commonly owned (point 7).

The Examiner does not make a double patenting rejection however, so applicants are at a loss as to how to proceed on this issue. With respect to points 7 and 8, however, the Examiner is clearly and unequivocally wrong.

The '474 patent and the present application share the same priority date. As was pointed out, supra, the Examiner has never contested applicants' priority claim. If a patent has the same priority date as a pending application, then it cannot serve as prior art, and point 7 is moot.

Given the confusion engendered by the presentation in points 5 and 6, applicants do not know how to proceed, but so as to avoid the re-opening of prosecution submit a terminal disclaimer and call upon the Examiner to clarify the record on this point.

IX CONCLUSION

For all of the reasons set forth supra, as well as the materials submitted herewith, it is believed that the rejections made under 35 U.S.C. § 112, first paragraph, holding the claims to fail to satisfy the written description and enablement requirements are improper and should be reversed.

To the extent that the most recent Office Action presents an inchoate double patenting rejection, this is believed moot in view of the terminal disclaimer filed concurrently herewith.

Respectfully submitted,

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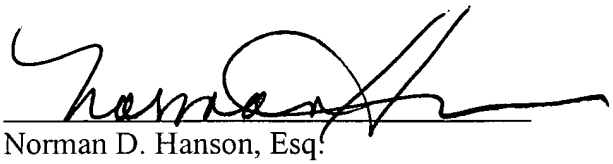

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Enclosures: **Listing of Claims on Appeal**
Partial Listing of Literature on MAGE TRAPs
Terminal Disclaimer

LISTING OF CLAIMS ON APPEAL

183. An isolated, MAGE tumor rejection antigen precursor protein, wherein said protein is encoded by a nucleic acid molecule, the complementary sequence of which hybridizes to SEQ ID NO: 8 at 0.1xSSC, 0.1% SDS, wherein said tumor rejection antigen precursor is obtainable from melanoma cells.

184. The isolated tumor rejection antigen precursor protein of claim 183, the amino acid sequence of which comprises the amino acid sequence set forth in SEQ ID NO: 26.

185. The isolated tumor rejection antigen precursor protein of claim 183, wherein said protein is a human protein.

186. Composition comprising the isolated tumor rejection antigen precursor protein of claim 183, and a pharmaceutically appropriate ingredient.

187. Composition comprising the isolated tumor rejection antigen precursor protein of claim 184, and a pharmaceutically appropriate ingredient.

188. Composition comprising the isolated tumor rejection antigen precursor protein of claim 185, and a pharmaceutically appropriate ingredient.

189. The composition of claim 186, in the form of a vaccine.

190. The composition of claim 187, in the form of a vaccine.

191. The composition of claim 188, in the form of a vaccine.

REFERENCES RELATING TO TRAPS

MAGE	HLA	Peptide Sequence	Position	Reference
MAGE-1	A1	EADPTGHSY	161-169	Traversari et al. J Exp Med. 1992 Nov 1;176(5):1453-7.
	A3	SLFRAVITK	96-104	Chaux P et al. J Immunol. 1999 Sep 1;163(5):2928-36.
	A24	NYKHCFPEI	135-143	Fujie T et al. Int J Cancer. 1999 Jan 18;80(2):169-72.
	A68	EVYDGREHSA	222-231	Chaux P et al. J Immunol. 1999 Sep 1;163(5):2928-36.
	B7	RVRFFFPSL	289-298	Luiten R et al. Tissue Antigens. 2000 Feb;55(2):149-52.
	B35	EADPTGHSY	161-169	Luiten RM et al.Tissue Antigens. 2000 Jul;56(1):77-81
	B37	REPVTKAEML	127-136	Tanzarella S et al. Cancer Res. 1999 Jun 1;59(11):2668-74.
	B53	DPARYEFLW	258-266	Chaux P et al. J Immunol. 1999 Sep 1;163(5):2928-36.
	Cw2	SAFPTTINF	62-70	Chaux P et al. J Immunol. 1999 Sep 1;163(5):2928-36.
	Cw3	SAYGEPRKL	230-238	Chaux P et al. J Immunol. 1999 Sep 1;163(5):2928-36.
	Cw16	SAYGEPRKL	230-238	van der Bruggen P et al. Eur J Immunol. 1994 Sep;24(9):2134-40.
	DR13	LLKYRAREPVTKAE	114-127	Chaux P. et al. J Exp Med. 1999 Mar 1;189(5):767-78.
	DR15	EYVIKVSARVRF	281-292	Chaux P et al. Eur J Immunol. 2001 Jun;31(6):1910-6.
MAGE-2	A2	YLQLVFGIEV	157-166	Kawashima I et al.Hum Immunol. 1998 Jan;59(1):1-14.
	A24	EYLQLVFGI	156-164	Tahara K et al. Clin Cancer Res. 1999 Aug;5(8):2236-41.
	B37	REPVTKAEML	127-136	Tanzarella S et al. Cancer Res. 1999 Jun 1;59(11):2668-74.

	DR13	LLKYRAREPVTKAE	121-134	Chaux P et al. J Exp Med. 1999 Mar 1;189(5):767-78.
MAGE-3	A1	EVDPIGHLY	168-176	Gaugler B et al. J Exp Med. 1994 Mar 1;179(3):921-30
	A2	FLWGPRALV[d]	271-279	van der Bruggen P et al. Eur J Immunol. 1994 Dec;24(12):3038-43.
	A2	KVAELVHFL	112-120	Kawashima I et al. Hum Immunol. 1998 Jan;59(1):1-14.
	A24	IMPKAGLLI	195-203	Tanaka F et al. Cancer Res. 1997 Oct 15;57(20):4465-8.
	A24	TFPDLESEF	97-105	Oiso M et al. Int J Cancer. 1999 May 5;81(3):387-94.
	B18	MEVDPIGHLY	167-176	Bilsborough J et al. Tissue Antigens. 2002 Jul;60(1):16-24.
	B35	EVDPIGHLY	168-176	Schultz ES et al. Tissue Antigens. 2001 Feb;57(2):103-9.
	B37	REPVTKAEML	127-136	Tanzarella S et al. Cancer Res. 1999 Jun 1;59(11):2668-74.
	B40	AELVHFLLL[i]	114-122	Schultz ES et al. J Exp Med. 2002 Feb 18;195(4):391-9.
	B44	MEVDPIGHLY	167-176	Herman J et al. Immunogenetics. 1996;43(6):377-83.
	B52	WQYFFPVIF	143-151	Russo V et al. Proc Natl Acad Sci U S A. 2000 Feb 29;97(5):2185-90.
	DP4	TQHFVQENYLEY	247-258	Schultz ES et al. Cancer Res. 2000 Nov 15;60(22):6272-5
	DR1	ACYEFLWGPRALVETS	267-282	Zhang Y et al. J Immunol. 2003 Jul 1;171(1):219-25.
	DR4	VIFSKASSSLQL	149-160	Kobayashi H et al. Cancer Res. 2001 Jun 15;61(12):4773-8
	DR7	VIFSKASSSLQL	149-160	Kobayashi H et al. Cancer Res. 2001 Jun 15;61(12):4773-8.
	DR11	TSYVKVLHHMVKISG	281-295	Manici S et al. J Exp Med. 1999 Mar 1;189(5):871-6.
	DR11	GDNQIMPKAGLLIIV	191-205	Consogno G et al. Blood. 2003 Feb 1;101(3):1038-44. Epub 2002 Sep 19.

	DR13	AELVHFLLLKYRAR	114-127	Chaux P et al. J Exp Med. 1999 Mar 1;189(5):767-78.
	DR13	LLKYRAREPVTKAE	121-134	Chaux P et al. J Exp Med. 1999 Mar 1;189(5):767-78.
MAGE-4	A1	EVDPASNTY[j]	169-177	Kobayashi T et al. Tissue Antigens. 2003 Nov;62(5):426-32.
	A2	GVYDGREHTV	230-239	Duffour MT et al. Eur J Immunol. 1999 Oct;29(10):3329-37.
	B37	SESLKMIF	156-163	Zhang Y Tissue Antigens. 2002 Nov;60(5):365-71.
MAGE-6	A34	MVKISGGPR	290-298	Zorn E at al. Eur J Immunol. 1999 Feb;29(2):602-7.
	B37	REPVTKAEML	127-136	Tanzarella S et al. Cancer Res. 1999 Jun 1;59(11):2668-74.
	DR13	LLKYRAREPVTKAE	121-134	Chaux P et al. J Exp Med. 1999 Mar 1;189(5):767-78.
MAGE-10	A2	GLYDGMEHL	254-262	Huang LQ et al. J Immunol. 1999 Jun 1;162(11):6849-54
	B53	DPARYEFLW	290-298	Chaux P et al. J Immunol. 1999 Sep 1;163(5):2928-36.
MAGE-12	A2[9]	FLWGPRALV[e]	271-279	van der Bruggen P et al. Eur J Immunol. 1994 Dec;24(12):3038-43.
	Cw7	VRIGHLYIL	170-178	Heidecker L et al J Immunol. 2000 Jun 1;164(11):6041-5.
	DR13	AELVHFLLLKYRAR	114-127	Chaux P et al. J Exp Med. 1999 Mar 1;189(5):767-78.